Distinct roles for fibroblast growth factor signaling in cerebellar development and medulloblastoma.

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Public Summary:

Cerebellar granule neurons are the most abundant neurons in the brain, and a critical element of the circuitry that controls motor coordination and learning. In addition, granule neuron precursors (GNPs), from which cerebellar granule neurons develop, are thought to be involved in the development of medulloblastoma, the most common malignant brain tumor in children. Thus, understanding the signals that control the growth and development of GNPs has important implications for neurobiology and neuro-oncology. Our previous studies have shown that growth of GNPs is regulated by a factor called Sonic hedgehog (Shh), whose aberrant activation can lead to medulloblastoma. Moreover, we have demonstrated that the effects of this factor on the growth of GNPs and medulloblastoma cells can be blocked by a protein called basic fibroblast growth factor (bFGF). But while the growth-promoting effects of Shh have been confirmed in tumor-bearing animals, the inhibitory effects of bFGF have not been. In this study we sought to determine if bFGF can inhibit the growth of medulloblastoma in mice. Importantly, we found that treatment of medulloblastoma cells with bFGF prevents them from forming tumors in mice, and inoculation of tumor-bearing mice with bFGF markedly inhibits tumor growth. These results suggest that activators of FGF signaling may be useful for targeting and treating medulloblastoma and other Shh-dependent tumors.

Scientific Abstract:

Cerebellar granule neurons are the most abundant neurons in the brain, and a critical element of the circuitry that controls motor coordination and learning. In addition, granule neuron precursors (GNPs) are thought to represent cells of origin for medulloblastoma, the most common malignant brain tumor in children. Thus, understanding the signals that control the growth and differentiation of these cells has important implications for neurobiology and neurooncology. Our previous studies have shown that proliferation of GNPs is regulated by Sonic hedgehog (Shh), and that aberrant activation of the Shh pathway can lead to medulloblastoma. Moreover, we have demonstrated that Shh-dependent proliferation of GNPs and medulloblastoma cells can be blocked by basic fibroblast growth factor (bFGF). But while the mitogenic effects of Shh signaling have been confirmed in vivo, the inhibitory effects of bFGF have primarily been studied in culture. Here, we demonstrate that mice lacking FGF signaling in GNPs exhibit no discernable changes in GNP proliferation or differentiation. In contrast, activation of FGF signaling has a potent effect on tumor growth: treatment of medulloblastoma cells with bFGF prevents them from forming tumors following transplantation, and inoculation of tumor-bearing mice with bFGF markedly inhibits tumor growth in vivo. These results suggest that activators of FGF signaling may be useful for targeting medulloblastoma and other Shh-dependent tumors.Oncogene advance online publication, 8 October 2012; doi:10.1038/onc.2012.440.